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Isoniazid-Associated Hepatitis

Serum Enzyme Determinations and Histologic Features

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A prospective study of 208 patients treated for up to 12 months with isoniazid (INH®) for tuberculosis prophylaxis was made. Levels of serum glutamic oxaloacetic acid transaminase (SGOT) became elevated in 20 percent of the adults followed and in 30 percent predominantly nonspecific symptoms developed, in 11 percent simultaneously with SGOT elevation; SGOT levels became elevated in two of 33 children and 1 was symptomatic. Mild SGOT elevations in asymptomatic adults were self-limited; however, a small percentage of symptomatic adults showed prolonged SGOT elevation for months after INH was completed. Results of liver biopsy studies in the early stages of SGOT elevation generally showed portal and periportal lymphocytic infiltrations with lesser numbers of plasma cells, neutrophils and eosinophils.

DOCUMENTATION OF THE therapeutic and prophylactic effectiveness of isoniazid (INH®) as an antituberculous agent has been well established,[1] as has its toxicity in a variety of organ systems.[2,3] Toxic hepatic injury with fatty degeneration after large doses of INH was shown in dogs in 1952.[4] Hepatitis associated with the administration of INH in the usual doses of 3 to 5 mg per kg of body weight per day in adults not also receiving para-aminosalicylic acid or streptomycin or both has recently been documented.[5-16]

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Five patients with INH-associated hepatitis were studied at Santa Clara Valley Medical Center from September 1970 through October 1971.[5] These cases in addition to other reports of INH-associated hepatitis[6,7] led us to initiate a prospective study to evaluate the frequency and severity of physiologic, histologic and symptomatic features of hepatitis and the possible role of associated medical conditions in patients prophylactically receiving INH.

Methods

Isoniazid therapy (3 to 5 mg per kg of body weight per day given orally) was begun in all patients seen in the Tuberculosis Clinic of the Santa Clara County Health Department between October 1971 and March 1972 who met the following

ABBREVIATIONS USED IN TEXT
HAA®=hepatitis-associated antigen
INH=isoniazid
SGOT=serum glutamic oxaloacetic transaminase
SGPT=glutamic pyruvic transaminase

criteria for chemoprophylaxis with INH: (1) recent conversion of tuberculin skin test results from negative to positive or (2) positive tuberculin test and recent contact with tuberculosis patients deemed infectious. No patient was excluded because of any underlying medical illness—including diabetes mellitus, obesity, history of liver disease, seizure disorders, pregnancy and alcohol abuse. General clinical evaluation, a tuberculin skin test, a roentgenogram of the chest and a baseline serum glutamic oxaloacetic transaminase (SGOT) measurement done before institution of INH therapy were required before inclusion in the study. Clinical evaluation and SGOT determination were repeated 1, 2, 3, 6, 9 and 12 months subsequently. If an SGOT level became elevated, serum bilirubin, alkaline phosphatase, glutamic pyruvic transaminase (SGPT) and hepatitis-associated antigen (HAA) were also measured simultaneously. Liver biopsies were done on the first eight patients in whom results were abnormal for two or more consecutive SGOT measurements, and on one additional patient in whom there were sustained SGOT elevations for a year after completion of therapy.

All patients were treated for one year. Patients who had at least two measurements of SGOT levels obtained within the first four months of therapy plus at least two levels during the subsequent eight months were considered to have had adequate one year follow-up. Isoniazid was discontinued when overt clinical hepatitis developed as well as when clinical evidence of toxicity to other organ systems occurred.

Results

Of the 208 patients treated with INH, ranging from 1 to 70 years of age, 19 were excluded from the study because of inadequate evaluation. Of the remaining 189 (156 adults and 33 children), 118 (63 percent) were followed for the full 12 months of INH therapy or until elevated SGOT levels returned to the normal range after discontinuation of INH. In the remaining 71 patients, at least two measurements of SGOT levels were obtained during the first four months but the minimum number required for adequate one year follow-up was not obtained. Clinical signs and symptoms of hepatitis were generally nonspecific (Table 1). Elevation of SGOT occurred in 20 (43 percent) of the 47 symptomatic adults, in 17 (16 percent) of the 109 asymptomatic patients and in 25 (18 percent) of the 142 patients without history of alcohol abuse.

Adults

Elevated SGOT levels before INH therapy: Six patients had elevated SGOT levels before initiation of INH therapy (Table 2). Two were known alcohol abusers and had mildly elevated serum bilirubin levels before treatment; SGOT levels remained elevated in one for 13 weeks of INH therapy—at which time the patient was lost to follow-up—and in the other patient, they returned to and remained within normal limits during INH therapy. One patient in whom a slightly elevated pretreatment level of SGOT was noted was a 19-year-old woman with a history of hepatitis who was on oral contraceptive therapy; the level returned to and remained within normal limits during INH therapy. In one 34-year-old woman (case 1, addendum) who was on oral contraceptive therapy, SGOT levels remained mildly elevated until week 22 of INH administration—at which time icterus and other symptoms of INH-associated hepatitis developed. The remaining two had no pertinent medical history to account for the enzyme elevations; the SGOT level returned to the normal range during 12 months of INH therapy in one and fluctuated but became normal by completion of therapy in the other.

Transient SGOT elevation during INH therapy:

TABLE 1.—*Signs and Symptoms in 156 Adults Receiving Isoniazid (INH®)*

*Symptoms**	*Number of Patients*	*Percent*
Headache	13	8.4
Myalgias	12	7.7
Malaise-fatigue	11	7.0
Abdominal discomfort	9	5.8
"Dark urine"	8	5.1
Nausea	7	4.5
Hepatomegaly	7	4.5
Arthralgias	6	3.8
Dizziness	6	3.8
Rash	6	3.8
Anorexia	5	3.2
TOTAL	47	30.0

*The following symptoms were noted in <3 percent of the patients: diaphoresis, pruritus, vomiting, visual abnormalities, diarrhea, dysesthias, irritability, fever and icterus (one patient).

TABLE 2.—*Summary of INH-treated Patients with SGOT Elevation*

	Sustained SGOT elevations (19 patients)	*Transient SGOT elevations (12 patients)*	*Pre-INH SGOT elevations (6 patients)*
Weeks of INH before elevation	3 to 40 weeks	2 to 33 weeks	
Peak SGOT (R-F units)*	47 to 179 units	44 to 84 units	65 to 282 units
Premature INH discontinuation	5 patients	1 patient	2 patients
Failure of SGOT to return to normal levels	6 patients: 4 with early elevations were lost to follow-up while levels still elevated; in 1 still elevated 5 months after INH completed; in 1 still elevated 1 year after INH completed—amyloid on liver biopsy. Returned to normal in 6 patients at or shortly after completion of INH	All normal by the end of 1 year of INH	In 1 elevations maintained through 13 weeks when lost to follow-up; 1 only after icterus led to INH discontinuation at 22 weeks

*Reitman-Frankel Units, normal less than 40 units.[17]
INH®=isoniazid.
SGOT=serum glutamic oxaloacetic acid transaminase

TABLE 3.—*Frequency of SGOT Elevations in Subgroups According to Underlying Medical Condition**

Subgroups	*Affected Number*	*Total Number Patients*	*Percent with SGOT Elevation*
Pregnancy	0	6	0
Diabetes	3	12	25
Previous hepatitis	1	4	25
Obesity	10	33	30
Alcohol abusers	7	14	50

*A single patient may have had one or more of the underlying medical conditions; however, there was no overlap in the patients with previous hepatitis.

Twelve patients with normal pretreatment SGOT levels had single or nonconsecutive elevations of SGOT during therapy (Table 2). In the ten with a single SGOT elevation, the abnormal level occurred between weeks 5 and 13 in six and between weeks 27 and 33 in four. The nonconsecutive elevations in the two patients occurred from weeks 2 to 16. Three of the 12 were alcohol abusers: in one, dark urine occurred at five weeks but serum bilirubin, alkaline phosphatase and SGPT levels were normal and HAA was negative; in the second, there were tender hepatomegaly, spider angiomata and an elevation of SGOT, SGPT and alkaline phosphatase and normal bilirubin at eight weeks, and in the third, SGOT was slightly elevated on one occasion.

In one patient in whom there were nonconsecutive SGOT elevations, headaches, arthralgia, myalgias, an SGOT level of 68 units and mildly elevated alkaline phosphatase occurred two weeks after starting INH; INH was discontinued for three days and then reinstituted at 2 mg per kg of body weight per day temporarily before returning to the previous dosage. The SGOT returned to normal levels except for a single mild elevation at 12 weeks. The patient was able to complete 12 months of INH therapy without further complication.

Persistent SGOT elevation during INH therapy: In 19 patients in whom pretreatment SGOT levels were normal, there were two or more consecutive SGOT elevations, 18 within 3 to 20 weeks of therapy and one at 40 weeks. Of 11 patients in whom SGPT was measured, eight had SGPT levels higher than the SGOT measurement. Alkaline phosphatase and bilirubin were usually within normal limits. In all 16 patients tested, HAA was negative.

Percutaneous liver biopsy was done in eight patients. In five, nonspecific hepatitis was evidenced by varying degrees of portal and lobular infiltration with predominant lymphocytes but with some plasma cells, neutrophils and eosinophils. Slight portal fibrosis and early bile duct proliferation were found in another patient (Case 2, addendum), and pronounced macrovesicular and mild microvesicular fatty metamorphosis were noted in the liver of a slender patient without history of alcohol abuse in whom there had been persistent elevation of SGOT for five months after completion of a year of INH therapy. In the eighth patient (Case 3, addendum), SGOT levels increased to 52 units at five weeks and to 68 units at nine weeks of INH therapy, and continued to remain mildly elevated for a year after completion of 12 months of INH. Results of liver biopsy a year after completion of INH therapy showed

amyloidosis, moderate fatty metamorphosis and mild fibrosis.

Subgroup analysis: Subgroups of adult patients according to pregnancy, diabetes mellitus, previous hepatitis, obesity and alcohol abuse were analyzed (Table 3).

Children

In the INH-treated children, SGOT abnormalities developed in two of the 33. In one, the increase was associated with an allergic diathesis, and in the other the level increased to 57 units just before completion of 12 months of INH therapy but returned to the normal range one month later.

Discussion

Three prospective studies on the hepatic abnormalities associated with INH chemoprophylaxis (Table 4) have been reported since 1969.[6,13,14] In the largest series,[14] neither SGOT nor other liver function tests were done until most patients had received INH for five to eight months, whereas in our series and those of others,[6,13] elevations appeared much earlier. The ranges and peaks of SGOT elevations did not vary significantly in the four studies.

Of the 156 adults in our series, SGOT elevations and symptoms of hepatitis were noted in 11 percent and these were considered to have INH-associated hepatitis. This incidence is higher than those of other studies[6,13,14] and may partially reflect our heterogeneous population in which no attempt was made to exclude patients with underlying medical illnesses.

The symptoms seen in patients receiving INH were mostly nonspecific. Abdominal discomfort, vomiting and dizziness were as common in patients with normal SGOT levels as in those with elevated SGOT levels, suggesting that they were pharmacologic side-effects of INH therapy. The presence of rash, fever and eosinophilia suggests a hypersensitivity (immunologic) response, which may play a role in the mechanisms of INH-associated hepatitis.[3,8,9,18] Overt signs of hepatitis were usually late manifestations of INH-associated hepatitis in our patients. Although anicteric viral hepatitis cannot be excluded in any of the patients, the temporal relationship with the initiation of INH therapy, the negative HAA, the lack of known exposure to hepatitis, and the return of SGOT levels to normal values after discontinuation of INH strongly implicate this drug as the causative agent.

TABLE 4.—*Comparative Data in Prospective INH Chemoprophylactic Studies*

	Scharer et al[6]	*Byrd et al*[13]	*Bailey et al*[14]	*Lewis et al*
Number of patients	90 patients	160 patients	427 patients*	189 patients
Population	Hospital employees (New York)	Military personnel (Illinois, Colorado and Maryland)	Hospital employees (Louisiana)	Tuberculosis Clinic (Santa Clara County, California)
Age of patients (yr)	Adults (average 39)	Adults (average 36 males; 38 females)	Adults (range 19-65)	156 adults (average 39 males; 35 females)	33 children (average 8.3)
Total no. of patients with SGOT elevations	11 (12.2%)	42 (26.2%)	37 (8.7%)	32 (20.6%)†	2 (6.1%)
Symptomatic	2 (2.2%)	9 (5.6%)	5 (1.2%)	18 (11.5%)†	1 (3%)
Asymptomatic	9 (10%)	37 (20.6%)	32 (7.5%)	14 (9.4%)	1 (3%)
SGOT range	65 to 160 R-F units	50 to 1,400 units	50 to 940 mμ/ml	44 to 282 R-F units	57 to 61 R-F units
Jaundice present	0	0	3	1	0
Liver biopsies described	1	0	2	9	0
Total no. of cases of INH discontinuance	2 (2.2%)	16 (10%)	18 (4.2%)	13 (8.7%) (5 medically)	4 (12%) (1 medically)
Pre-INH SGOT measured	Yes	Yes	No	Yes	Yes
Frequency of SGOT sampling	Weekly	1, 3, 6, 9 and 12 months	None until monthly sampling after 5-8 months INH	1, 2, 3, 6, 9 and 12 months	1, 2, 3, 6, 9 and 12 months

*Early months data missing.
†Includes 1 patient with elevated pretreatment SGOT who progressed to icterus at 22 weeks (Case 1, addendum).
INH@=isoniazid.
SGOT=serum glutamic oxaloacetic acid transaminase
R-F units=Reitman-Frankel units

A variety of histopathologic lesions have previously been reported in INH-associated hepatitis including noncaseating granulomata,[5] cholestasis,[5,16] bridging necrosis,[18] fibrosis,[14] chronic active hepatitis[14] and massive hepatic necrosis[14,15]—as well as the more typical hepatocellular changes resembling viral hepatitis[5,6,8,11,15,19] seen in most of our patients in whom biopsies were done. Most liver biopsies in our series were done early in the course of treatment when SGOT elevations were not as high; peak SGOT levels occurred 2 to 21 weeks after the biopsies were done in five of the six patients in whom INH therapy was continued.

Conclusions

Thirty percent of the 156 adults treated with INH were symptomatic. Eleven percent had concomitant SGOT elevations and were considered to have INH-associated hepatitis. Of the adults with SGOT elevations and no symptoms of hepatitis (9 percent), three in whom liver biopsy studies were done had histologic abnormalities. In the absence of other obvious causes, patients in this group probably had subclinical INH-associated hepatitis. Mild SGOT elevations in asymptomatic patients were self-limited.

When symptoms are present, SGPT may be a more sensitive indicator of INH-associated hepatitis than SGOT, with bilirubin and alkaline phosphatase frequently remaining normal until late in the course of the disease. In a small percentage of the symptomatic patients, there were prolonged elevations of SGOT levels even after discontinuance of INH therapy that were still elevated in some at the end of follow-up (one year).

Because of these findings, we recommend that monthly clinical evaluations be made in patients receiving INH. In symptomatic patients, liver function tests to include SGOT, SGPT, bilirubin, alkaline phosphatase and HAA should be done and in those with prolonged elevation of hepatic enzymes, or elevated bilirubin or alkaline phosphatase, INH administration should be discontinued. Liver biopsy may be indicated in this group particularly if the results of liver function tests do not return to normal values after INH is discontinued.

Addendum: Selected Case Histories

CASE 1. A slightly obese 34-year-old woman reported transient cough and myalgias one month before visiting the Tuberculosis Clinic in January 1972. On chest roentgenogram, no abnormalities were noted; SGOT and SGPT were 58 and 84 units, respectively, with normal bilirubin and alkaline phosphatase levels and no history of liver disease or alcohol abuse. Oral contraceptive pills and diphenhyramine hydrochloride (Benadryl®) were the only medications being taken by the patient. Treatment with INH was begun. Two weeks later, anorexia and nausea occurred. Administration of INH was discontinued and when symptoms resolved three days later, it was resumed at the same dosage. During week five the patient was asymptomatic, HAA was negative but SGOT level was 65 units, SGPT 42 units and results of liver biopsy showed pronounced macrovesicular fatty metamorphosis, patchy microvesicular fat as well as focal portal and periportal necrosis with lymphocytes, plasma cells and some eosinophils. Because there were no symptoms of INH toxicity at this time, INH was continued. During week 22, anorexia, fatigue, dark urine, acholic stools, scleral icterus and tender hepatomegaly developed; SGOT was 282 units, total bilirubin 6.2 mg per 100 ml, alkaline phosphatase 4.6 Bodansky units (normal 1 to 4.5) and HAA negative. Isoniazid was discontinued and the signs and symptoms gradually subsided; SGOT was 65 units eight weeks after cessation of INH therapy and within normal limits 20 weeks after cessation.

CASE 2. A 53-year-old chronic alcohol abuser with a history of emphysema was seen in the Tuberculosis Clinic in December 1971 because of positive findings on a tuberculin skin test. Aortoiliac endarterectomy for claudication had been done in July 1971. The SGOT levels measured in October and December 1971 before INH therapy were within normal limits. Two weeks after starting INH, bilateral ankle pain developed and progressed to ischemic changes in the feet, a temperature of 38.3°C (101°F) developed and the patient was admitted to the hospital. On roentgenograms of the chest, bilateral perihilar pneumonitis was noted, although sputa grew normal flora. Leukocyte count was 20,000 per cu mm with a left shift, SGOT 132 units, total bilirubin 2.2 mg per 100 ml, alkaline phosphatase 66 King Armstrong units (normal <17), creatinine 2.1 mg per 100 ml and prothrombin time 60 percent of normal activity. Isoniazid was discontinued and parenteral penicillin, 600,000 units every six hours for seven days, and oral tetracycline, 500 mg every six hours for four days, were administered.

Findings on percutaneous liver biopsy on day seven showed increased portal connective tissue,

mild chronic inflammatory infiltrate and early bile duct proliferation. The pneumonitis cleared. Results of liver function tests were within normal limits one month after admission to hospital.

CASE 3. A 65-year-old slightly obese man was seen in the Tuberculosis Clinic in March 1972 because of positive response to a tuberculin skin test. He reported a history of drinking a glass of wine with dinner until INH therapy was begun. The level of SGOT, which was within normal limits before INH, increased to 52 units by week five and continued to increase to twice normal values during the year of treatment. The only symptoms were mild chills and sweats during the first few months of therapy. During the year after discontinuance of INH, SGOT and SGPT levels remained approximately twice normal, and findings on liver biopsy included amyloidosis, moderate fatty metamorphosis, mild bile duct stasis and mild fibrosis. On complete blood cell count, no abnormalities were noted except for slight erythrocytic macrocytosis and rare target cells. Mild lymphocytosis and plasmacytosis were noted on bone marrow biopsy specimens, and cultures for acid-fast bacilli were negative. Urine was negative for Bence-Jones protein. Serum bilirubin and alkaline phosphatase levels and protein electrophoretic values were normal. Rheumatoid arthritis titer was negative. Prothrombin time was 60 percent of normal activity.

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